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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,656	10/24/2003	Igor Dozmorov	OMRF:013US	9649

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EXAMINER

SKOWRONEK, KARLHEINZ R

ART UNIT	PAPER NUMBER
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1631

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06/20/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/693,656	Applicant(s) DOZMOROV ET AL.	
	Examiner KARLHEINZ R. SKOWRONEK	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 March 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-9 and 11-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-9 and 11-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Status

Claims 1, 3-9 and 11-13 are pending.

Claims 2 and 10 are cancelled.

Claims 1, 3-9 and 11-13 are being examined.

Specification

Response to Arguments

Applicant's arguments, see remarks p. 1, filed 26 March 2008, with respect to the objection to the specification have been fully considered and are persuasive. The objection to the specification has been withdrawn in view of applicants' amendment.

Claim Rejections - 35 USC § 112

Response to Arguments

Applicant's arguments, see Remarks p. 1, filed 26 March 2008, with respect to the rejection of claims 1, 3-9, and 11-13 as introducing new matter under 35 USC 112, First Paragraph have been fully considered and are persuasive. The rejection of claims 1, 3-9 and 11-13 has been withdrawn.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 3-9, 11, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear with respect to the outliers in the adjusting step because the claim fails to indicate how the identified outliers are linked with the rescaling step in adjusting. For the purpose of examination, the claim will be interpreted to include an step of excluding the identified outliers from the rescaling process. Claims 3-9, 11, and 12 are also rejected because they depend from claim 1, and thus contain the above issues due to said dependence.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-6, 8-9, and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu (IDS file 2/27/04, Entry C13), in view of Shaffer (Annual Review of Psychology, Vol. 46, p. 561-584, 1995), and in view of Cole et al. (Prenatal Diagnosis, Vol. 19, p. 351359, 1999).

The claims are directed to a method of associative analysis comprising the collection of a plurality of expression profiles from a control and experimental group; normalizing the control and experiment groups relative to the background; adjusting the expression profiles by rescaling the control and experimental groups to an average of the control group; identifying similarly and differential expressed genes, the differentially expressed genes are identified using a paired T-Test and an "associative T-Test"; determining a classification for the identified differentially expressed genes where gene identified by the T-test but not the Associative T-test are likely false positives, gene identified by the T-test and the associative T-test are real positives and genes identified by the Associative T-test but not the T-Test are potential positives; and outputting the classified real positives to a user. In some embodiments, the adjusting expression profiles further comprises regression analysis. In some embodiments, adjusting further

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comprising selected equally expressed genes as a homogenous family of genes with normally distributed residuals measured as deviations from a regression line that is calculated against an average profile.

As defined in the specification at p. 13, lines 10-11, an "associative T-test" is a standard T-test applied to the comparison of expression deviations. The "associative T-test" as defined in specification is also known in the art as an F-test.

Wu shows a method of analyzing gene expression profiles. Wu et al. shows the collection of a plurality of expression profiles from a control and experimental group (figure 1 and p. 55, col. 1). Wu et al. shows normalizing the control and experimental profiles (p. 56, col. 1) relative to background. Wu shows that expression profiles are scaled to an average of the control by scaling the control by $\sqrt{\beta}$ and the experimental by $\frac{1}{\sqrt{\beta}}$ (p. 56, col. 1). Wu shows that differentially expressed genes are identified using the T-test (p. 58, col. 1). In some embodiments, Wu shows adjusting expression profiles further comprise regression analysis (p. 55, col. 2). In some embodiments, Wu shows adjusting further comprising selected equally expressed genes as a homogenous family of genes with normally distributed residuals measured as deviations from a regression line that is calculated against an average profile (p. 56, col. 2). Wu shows that lower values for variability lead to higher T values and a larger number of false positives suggestive of the comparison of values for variability. Wu shows the F-test is a comparison of variances similar to the T-test as comparison of means (p. 60, col. 1). Wu shows the F-test is useful for identifying genes that are overexpressed or

underexpressed in any one of several conditions (p. 60, col. 1). Wu shows that the F-test identified genes are retested (p. 60, col. 1). Wu shows an embodiment in which outliers are removed (p.57, col. 2). In some embodiments, the reference group of genes is determined by an F-test (p. 60, col. 1).

Wu does not show the determining a classification for the identity of differentially expressed genes where gene identified by the T-test but not the Associative T-test are likely false positives, gene identified by the T-test and the associative T-test are real positives and genes identified by the Associative T-test but not the T-Test are potential positives.

Cole et al. shows that true positives are identified by significant T-test and F-test statistics (p. 353, col. 2). Cole et al. shows that true negatives are identified by lack of significant T-test and F-test values (p.353, col. 2)

Shaffer shows that when multiple pairwise t-test are considered the probabilities of false positives is additive, thereby reducing the power for testing individual hypotheses (p. 569). Shaffer shows that multistage test procedure, that is also performing the F-test, overcomes the problems of multiple pairwise comparisons (p. 569). Shaffer suggests that potential positives can be detected if only the F-test is significant (p. 574). Shaffer shows that type I error is also known as a false positive classification (p. 566). Shaffer shows that in cases where multiple comparisons are performed heterogeneity in the variance becomes a more serious concern. Shaffer points out that the variance of a particular comparison may be badly biased by the use

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of a common estimated value (p. 577). Shaffer's concern is interpreted as a classification of false positive if the T-test is significant but the F-test is not.

It would have been obvious to one of ordinary skill in the art to modify the gene analysis method of Wu with the combination analysis of T-test and F-test as described by Cole et al. and Shaffer because all the claimed elements were known, in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of the invention.

Claim 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu, in view of Shaffer, and in view of Cole et al. as applied to claims 1, 3-6, 8-9, and 11-13 above, and further in view of Jensen et al. (Bioinformatics, Vol. 16, No. 4, P. 326-333, 2000).

Claim 7 is directed to a method of array analysis that further comprises a Kolmogorov-Smirnov criterion.

Wu, in view of Shaffer, and in view of Cole et al. as applied to claims 1, 3-6, 8-9, and 11-13 above shows a method of array analysis.

Wu, in view of Shaffer, and in view of Cole et al. as applied to claims 1, 3-6, 8-9, and 11-13 above do not show a Kolmogorov-Smirnov criterion.

Jensen et al. shows a Kolmogorov-Smirnov (K-S) criterion (p. 328, col. 1).

Jensen et al. shows that the K-S has the advantage of finding patterns without the need for data clustering (p 332, col. 1).

It would have been obvious to one of ordinary skill in the art at the time of invention to modify the method for array analysis of Wu, in view of Shaffer, and in view of Cole et al. as applied to claims 1, 3-6, 8-9, and 11-13 above with the K-S criterion of Jensen et al. because Jensen et al. suggests that the K-S criterion has the advantage of finding patterns without the need for data clustering.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARLHEINZ R. SKOWRONEK whose telephone number is (571)272-9047. The examiner can normally be reached on Mon-Fri 8:00am-5:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

20 June 2008

/K. R. S./
Examiner, Art Unit 1631
/John S. Brusca/
Primary Examiner, Art Unit 1631